Supporting Information

Chemical Delivery System of MIBG to the Central Nervous System: Synthesis, ^{11}C-Radiosynthesis and *in Vivo* Evaluation

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Chemistry

All commercial reagents were used without further purification. The solvents were dried with appropriate desiccants and distilled prior to use or were obtained anhydrous from commercial suppliers. Silica gel (60, 230–400 mesh or 70–230 mesh) was used for column chromatography. Reactions were monitored by thin layer chromatography on silica gel precoated aluminium plates. UV light at 254 nm or $KMnO_4$ stains were used to visualize TLC plates. NMR spectra were recorded on a Bruker AVANCE 300 at 300 MHz (^1H), 75 MHz (^{13}C) and 282 MHz (^{19}F). Abbreviations used for peak multiplicities are s: singlet, d: doublet, t: triplet, q: quadruplet dd = doublet of doublet, br = broad and m: multiplet. Coupling constants *J* are in Hz and chemical shifts are given in ppm and calibrated with DMSO-d_6 or $CDCl_3$ (residual solvent signals). ^1H NMR spectra obtained in $CDCl_3$ were referenced to 7.26 ppm and in DMSO-d_6 to 2.50 ppm. ^{13}C NMR spectra obtained in $CDCl_3$ were referenced to 77.16 ppm and in DMSO-d_6 to 39.52 ppm. High Resolution Mass spectra analyses (HRMS) were performed by the Mass Spectrometry Laboratory on the University of Rouen. HRMS analyses were performed with a Waters LCT U Premier XE (ESI) spectrometer. Relative intensities are given. IR spectra were recorded on a PERKIN ELMER IRTF 1650 spectrometer. Absorption bands are given in cm^{-1}. Melting points of solid compounds (°C) were determined with a STUART SMP3 apparatus.

N-(3-iodobenzyl)-N'-(1-methyl-3-carbonyl-6,7-dimethoxy-1,4-dihydroquinoline)-guanidine (1b). Under nitrogen, BNAH[26] (7 mg, 0.03 mmol) was added to a solution of **2b** (20 mg, 0.03 mmol) in anhydrous dichloromethane (8 mL) and the mixture was protected from the light. After 12 h at 20°C, the solution was washed with water (3 x 8 mL), dried over $MgSO_4$

and evaporated under reduced pressure to afford **1b** (5 mg, 32%) as an orange solid. m. p. 109-111°C. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.70-7.24 (m, 7H), 4.40 (s, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 3.77 (s, 2H), 3.25 (s, 3H). IR (cm^{-1}): 1682, 1640, 1557, 1453, 1168, 1057, 694, 605. HRMS (ESI^+): calcd for $C_{21}H_{24}IN_4O_3[M+H]^+$ 507.0893; found 507.0876. MS/MS (ESI^+): m/z (%) = 507 (25%), 232 (100%). HPLC: Column: Phenomenex Gemini C18 5 µm 110 Å 250 x 4.6 mm, eluent: acetonitrile/sodium phosphate dibasic 10 mM (55/45), flow: 1 mL/min, λ: 254 nm, t_R = 6.9 min

N-(3-iodobenzyl)-N'-(1-methyl-3-carbonyl-7-methoxy-1,4-dihydroquinoline)-guanidine (1c). Under nitrogen, BNAH[26] (12 mg, 0.05 mmol) was added to a solution of **2c** (30 mg, 0.05 mmol) in anhydrous dichloromethane (10 mL). The resulting mixture was protected from the light and stirred at 20°C for 12 h. The organic layer was washed with water (3 x 10 mL), dried over $MgSO_4$ and evaporated under reduced pressure to yield **1c** (16 mg, 70%) as an orange solid. m. p.: 101-103°C. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.69 (s, 1H), 7.64 (d, J = 7.2 Hz, 1H), 7.55 (s, 1H), 7.37-7.29 (m, 3H), 7.10 (t, J = 7.6 Hz, 1H), 6.99 (d, J = 8.0 Hz, 1H), 4.41 (s, 2H), 3.79 (s, 3H), 3.74 (s, 2H), 3.21 (s, 3H). HRMS (ESI^+): calcd for $C_{20}H_{22}IN_4O_2$ $[M+H]^+$ 477.0788; found 477.0776. MS/MS (ESI^+): m/z (%) = 477 (22%), 202 (100%). IR (cm^{-1}): 1682, 1606, 1538, 1454, 1256, 1093, 694, 612. HPLC: Column: Phenomenex Gemini C18 5µm 110Å 250x4.6 mm, eluent: acetonitrile/ammonium acetate 10 mM (55/45), flow: 1 mL/min, λ: 254 nm, t_R = 9.3 min.

N-(3-iodobenzyl)-N'-(1-methyl-3-carbonyl-6,7-dimethoxyquinolinium)-guanidine trifluoromethane sulfonate (2b). Under nitrogen, methyl trifluoromethane sulfonate (15 µL, 0.12 mmol) was added to a solution of **5b** (50 mg, 0.10 mmol) in anhydrous dichloromethane (5 mL). The resulting solution was stirred at 20°C for 3 h. Diethyl ether (5 mL) was added. After 12 h at 4°C, the

precipitate formed was filtered, washed with diethyl ether and dried to give **2b** (40 mg, 60%) as a white solid. m. p.: 224-226°C. ^{1}H NMR (400.13 MHz, DMSO-d_6): δ 9.57 (s, 1H), 9.48 (s, 1H), 8.03 (s, 1H), 7.84 (s, 1H), 7.68 (s, 1H), 7.64 (d, J = 7.6 Hz, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.19 (t, J = 6.8 Hz, 1H), 4.73 (s, 1.2H), 4.63 (s, 3H), 4.48 (s, 0.8H), 4.17 (s, 3H), 4.04 (s, 3H). HRMS (ESI$^+$): calcd for $C_{21}H_{22}IN_4O_3$ [M]$^+$ 505.0737; found 505.0760. MS/MS (ESI$^+$): m/z (%) = 505 (19%), 488 (74%), 272 (100%). IR (cm^{-1}): 1612, 1531, 1431, 1240, 1221, 1162, 1024, 745, 693, 637. HPLC: Column: Phenomenex Gemini C18 5µm 110Å 250x4.6 mm, eluent: acetonitrile/sodium phosphate dibasic 10 mM (55/45), flow: 1 mL/min, λ: 254 nm, t_R = 5.0 min.

N-(3-iodobenzyl)-N'-(1-methyl-3-carbonyl-7-methoxyquinolinium)-guanidine trifluoromethane sulfonate (2c). Under nitrogen, methyl trifluoromethane sulfonate (15 µL, 0.13 mmol) was added to a solution of **7** (50 mg, 0.11 mmol) in anhydrous dichloromethane (5 mL). The mixture was stirred at 20°C for 3 h. Then, diethyl ether (5 mL) was added and after 1 h at 4°C, the precipitate formed was filtered, washed with diethyl ether and dried to yield **2c** (55 mg, 81%) as a white solid. m. p.: 137-139°C. ^{1}H NMR (400.13 MHz, DMSO-d_6): δ 9.73 (s, 1H), 9.60 (s, 1H), 8.55 (d, J = 9.6 Hz, 1H), 7.83 (s, 1H), 7.74-7.72 (m, 2H), 7.64 (d, J = 7.0Hz, 1H), 7.44 (d, J = 6.8 Hz, 1H), 7.19 (t, J = 7.2 Hz, 1H), 4.71 (s, 1.2H), 4.62 (s, 3H), 4.47 (s, 0.8H), 4.15 (s, 3H). HRMS (ESI$^+$): calcd for $C_{20}H_{20}IN_4O_2$ [M]$^+$ 475.0631; found 475.0632. MS/MS (ESI$^+$): m/z (%) = 475 (15%), 458 (100%), 242 (99%). IR (cm^{-1}): 1616, 1552, 1471, 1243, 1224, 1150, 1027, 784, 696, 637. HPLC: Column: Phenomenex Gemini C18 5µm 110Å 250x4.6 mm, eluent: acetonitrile/ammonium acetate 10 mM (55/45), flow: 1 mL/min, λ: 254 nm, t_R = 4.7 min.

2-[3-N-(tert-butyl)carbamoyl-prop-2-enyl]-7-methoxyquinoline-3-carboxylate (4d). Under nitrogen, NBI (200 mg, 0.84 mmol) was added to a mixture of 7-methoxy-3-quinoline carboxylic acid (170 mg, 0.84 mmol) and triethylamine (120 µL, 0.84 mmol) in anhydrous

dimethylformamide (2 mL). The mixture was stirred at 20°C for 12 h. The solution was poured on ice water (15 mL) and the resulting mixture was kept at 4°C for 2 h. The precipitate formed was filtered, washed with water and dried to yield **4d** (212 mg, 74%) as a yellow solid. m. p.: 146-148°C. ^{1}H NMR (400.13 MHz, CD_3OD): δ 9.32 (d, J = 2.4 Hz, 1H), 8.98 (d, J = 2.0 Hz, 1H), 7.99 (d, J = 8.8 Hz, 1H), 7.45 (d, J = 2.0 Hz, 1H), 7.35 (dd, J = 9.2, 2.8 Hz, 1H), 5.75 (d, J = 0.8 Hz, 1H), 4.01 (s, 3H), 2.12 (d, J = 0.8 Hz, 3H), 1.24 (s, 9H). ^{13}C NMR (100.6 MHz, CD_3OD): δ 165.6, 164.9, 163.9, 155.5, 152.6, 151.3, 140.9, 131.9, 123.6, 122.2, 121.9, 113.4, 107.3, 56.3, 51.9, 28.8, 21.0. HRMS (ESI$^+$): calcd for $C_{19}H_{23}N_2O_4$ [M+H]$^+$ 343.1658; found 343.1643. MS/MS (ESI$^+$): m/z (%) = 343 (44%), 244 (19%), 204 (12%), 186 (100%). IR (cm^{-1}): 1735, 1687, 1616, 1447, 1280, 1158, 739.

2,5-dioxopyrrolidin-1-yl quinoline-3-carboxylate (4e). Under argon, 3-quinolinecarboxylic acid **4a** (1 g, 5.77 mmol) and *N*-hydroxysuccinimide (664 mg, 5.77 mmol) were dissolved in 20 mL anhydrous acetonitrile. Di-2-pyridyl carbonate (1.25 g, 5.77 mmol) and 4-dimethylaminopyridine (70 mg, 0.57 mmol, 0.1 eq) were added. The mixture was stirred at 20°C during 24 hours. The solvent was removed by evaporation under reduced pressure and the residue was dissolved in 20 mL dichloromethane. The organic phase was washed with water (3×20 mL), and then dried over $MgSO_4$. Dichloromethane was removed by evaporation under reduced pressure to give **4e** as a white solid (1.37 g, 88%). m. p.: 182°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.48 (d, J = 2.2 Hz, 1H), 9.00 (d, J = 1.7 Hz, 1H), 8.20 (d, J = 8.7 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 7.91 (ddd, J = 8.5, 7.0, 1.5 Hz, 1H), 7.73–7.64 (m, 1H), 2.95 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.2, 160.9, 150.5, 149.5, 140.5, 133.3, 129.7, 129.5, 128.2, 126.4, 118.3, 25.7. HRMS (ESI$^+$): calcd for $C_{14}H_{11}N_2O_4$ [M+H]$^+$ 271.0719; found 271.0725. IR (cm^{-1}) 1776, 1721, 1204, 1072, 758.

N-(3-iodobenzyl)-N'-(3-carbonyl-6,7-dimethoxyquinoline)-guanidine (5b). MIBG was prepared from MIBG, HCl (270 mg, 0.86 mmol) and potassium *tert*-butyl oxide (115 mg, 1.03 mmol) in anhydrous dimethylformamide (5 mL). CDI (140 mg, 0.86 mmol) was added to a solution of 6,7-dimethoxy-3-quinoline carboxylic acid **4b** (200 mg, 0.86 mmol) in anhydrous dimethylformamide (4 mL). The mixture was stirred at 20°C for 1 h and then added to the freshly prepared MIBG solution. The resulting mixture was stirred at 20°C for 12 h. Afterwards, acetonitrile (10 mL) was added. After 2 h at 4°C, the precipitate formed was filtered. The resulting filtrate was dried under reduced pressure. The crude product was purified by chromatography on silica gel (dichloromethane/methanol from 100/0 to 97/3) to yield **5b** (150 mg, 36%) as a white solid. m.p.: 120-122°C. ^{1}H NMR (400.13 MHz, CD_3OD): δ 9.27 (s, 1H), 8.75 (s, 1H), 7.79 (s, 1H), 7.62 (d, J = 7.2 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.33 (s, 1H), 7.29 (s, 1H), 7.13 (t, J = 7.2 Hz, 1H), 4.66 (s, 1.2H), 4.47 (s, 0.8H), 4.00 (s, 3H), 3.97 (s, 3H). ^{13}C NMR (100.6 MHz, CD_3OD): δ 176.7, 155.5, 151.8, 150.5, 149.3, 146.8, 137.4, 131.5, 128.8, 127.7, 124.5, 107.6, 107.2, 72.3, 56.5, 44.9. HRMS (ESI^+): calcd for $C_{20}H_{20}IN_4O_3$ $[M+H]^+$ 491.0580; found 491.0604. MS/MS (ESI^+): m/z (%) = 491 (6%), 474 (87%), 258 (100%), 216 (38%). IR (cm^{-1}): 1610, 1587, 1449, 1237, 1055, 659, 619. HPLC: Column: Phenomenex Gemini C18 5µm 110Å 250x4.6 mm, eluent: acetonitrile/sodium phosphate dibasic 10 mM (55/45), flow: 1 mL/min, λ: 254 nm, t_R = 5.9 min.

N-(3-iodobenzyl)-N'-(3-carbonyl-7-methoxyquinoline)-guanidine (5c). MIBG was prepared from MIBG, HCl (104 mg, 0.33 mmol) and potassium *tert*-butyl oxide (45 mg, 0.40 mmol) in anhydrous dimethylformamide (4 mL). So, a solution of **4d** (100 mg, 0.33 mmol) in anhydrous dimethylformamide (3 mL) was added to the freshly prepared MIBG solution. The resulting solution was heated at 140°C for 7 h. Thereafter, the solvent was evaporated under reduced pressure and purified by chromatography on silica gel (dichloromethane/methanol

from 100/0 to 97/3) to afford compound **5c** (112 mg, 76%) as a white solid. m. p.: 82-84°C. ^{1}H NMR (400.13 MHz, CD_3OD): δ 9.38 (s, 1H), 8.77 (s, 1H), 7.81 (d, J = 8.8 Hz, 1H), 7.75 (s, 1H), 7.57 (d, J = 7.2 Hz, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.31 (d, J = 2.0 Hz, 1H), 7.20 (dd, J = 9.2, 2.4 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 4.61 (s, 1.2H), 4.44 (s, 0.8H), 3.92 (s, 3H). ^{13}C NMR (100.6 MHz, CD_3OD): δ 176.3, 163.7, 151.9, 151.3, 138.6, 137.3, 131.5, 130.7, 127.6, 123.9, 121.3, 106.9, 95.1, 56.1, 44.9. HRMS (ESI^+): calcd for $C_{19}H_{18}IN_4O_2[M+H]^+$ 461.0475; found 461.0457. MS/MS (ESI^+): m/z (%) = 461 (56%), 444 (100%), 228 (85%), 217 (10%), 186 (66%). IR (cm^{-1}): 1734, 1581, 1574, 1455, 1208, 1136, 775, 656. HPLC: Column: Phenomenex Gemini C18 5µm 110Å 250x4.6 mm, eluent: acetonitrile/ammonium acetate 10 mM (55/45), flow: 1 mL/min, λ: 254 nm, t_R = 6.6 min.

Tert-butyl (4-(3-(3-iodobenzyl)guanidino)-4-oxobutyl)carbamate (8a). Under argon, **6b** (326 mg, 1.60 mmol) and CDI (286 mg, 1.77 mmol, 1.1 eq) were dissolved in dry tetrahydrofuran (10 mL). The mixture was stirred at 20°C for 36 hours. Under argon, MIBG,HCl [28,29] (500 mg, 1.6 mmol) was placed in anhydrous tetrahydrofuran (10 mL) and sodium hydride (60% in oil, 128 mg, 3.2 mmol) was added. The mixture was heated at 50°C during 30 min. After cooling at room temperature, the solution resulting from **6b** was added and the new solution was stirred overnight at 20°C. The solvent was removed by vacuum and the residue was dissolved in dichloromethane (10 mL). The organic phase was washed with water (3×10 mL), dried over $MgSO_4$, filtered and concentrated to give **8a** as yellow oil (616 mg, 84%). ^{1}H NMR (300 MHz, MeOD): δ 7.71 (s, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.32 (d, J = 7.7 Hz, 1H), 7.12 (t, J = 7.7 Hz, 1H), 4.41 (s, 2H), 3.06 (t, J = 6.9 Hz, 2H), 2.27 (t, J = 7.5 Hz, 2H), 1.82–1.68 (m, 2H), 1.42 (s, 9H). ^{13}C NMR (75 MHz, MeOD): δ 162.9, 162.4, 158.2, 137.2, 131.4, 127.5, 95.2, 79.7, 78.9, 68.8, 54.8, 44.61, 41.1, 28.8, 27.4. HRMS (ESI^+): calcd for

$C_{17}H_{26}IN_4O_3$ $[M+H]^+$ 461.1050; found 461.1044; IR (cm^{-1}) 3332, 2972, 2926, 1683, 1566, 1512, 1364, 1162, 772.

4-(3-(3-iodobenzyl)guanidino)-4-oxobutan-1-aminium chloride (8b). Acetyl chloride (310 µL, 4.34 mmol) was added to a solution of 24 (100 mg, 0.22 mmol) in methanol (3 mL) and the mixture was stirred at 20°C during 1 h. The solution was evaporated under reduced pressure to yield **8b** (90 mg, 100%) as a yellow oil. ^{1}H NMR (400.13 MHz, CD_3OD): δ 7.76 (s, 1H), 7.72 (d, J = 7.7 Hz, 1H), 7.38 (d, J = 7.3 Hz, 1H), 7.19 (t, J = 7.9 Hz, 1H), 4.54 (s, 2H), 2.98 (t, J = 7.8 Hz, 2H), 2.70 (t, J = 6.4 Hz, 2H), 2.02 (qt, J = 7.2 Hz, 2H). ^{13}C NMR (100.6 MHz, CD_3OD): δ 174.5, 155.4, 142.7, 138.7, 137.5, 131.9, 127.9, 95.3, 45.4, 40.2, 31.5, 23.8. HRMS (ESI^+): calcd for $C_{12}H_{18}IN_4O$ $[M]^+$ 361.0525; found 361.0523. MS/MS (ESI^+): m/z (%) = 361 (100%), 276 (90%). IR (cm^{-1}): 2955, 1723, 1687, 1617, 1471, 691, 657.

4-(3-(3-iodobenzyl)guanidino)-4-oxobutan-1-aminium 2,2,2-trifluoroacetate (8b').

Under argon, **8a** (136 mg, 0.30 mmol) was dissolved in dry dichloromethane (4 mL) and the mixture was placed in an ice bath at -5°C. Anhydrous trifluoroacetic acid (0.45 mL, 5.91 mmol) was added dropwise and the mixture was stirred 1 hour in an ice bath. The solvent was removed by vacuum to give **8b'** as a translucent oil (137 mg, 98%). ^{1}H NMR (300 MHz, MeOD): δ 7.75 (s, 1H), 7.70 (d, J = 7.7 Hz, 1H), 7.37 (d, J = 7.6 Hz, 1H), 7.17 (t, J = 7.8 Hz, 1H), 4.52 (s, 2H), 3.02 (t, J = 7.5 Hz, 2H), 2.68 (t, J = 7.1 Hz, 2H), 2.07 – 1.94 (m, 2H). ^{13}C NMR (75 MHz, MeOD): δ 176.1, 162.9 (q, J = 35.5 Hz), 155.2, 140.3, 138.9, 138.4, 137.3, 131.8, 127.6, 95.3, 44.9, 39.8, 34.2, 22.8. ^{19}F NMR (282 MHz, MeOD): δ -75.85. HRMS (ESI^+): calcd for $C_{12}H_{18}IN_4O^+$ $[M^+]$ 361.0525; found 361.0164; IR (cm^{-1}) 2961, 1661, 1127, 1180, 721.

N-(3-iodobenzyl)-N'-[4-(3-carbonyl-quinoline)aminobutanoyl]-guanidine (9). NaOH 1M (925 µL, 0.92 mmol) was added to a solution of **8b** (366 mg, 0.92 mmol) in dimethylformamide (8.5 mL) and the mixture was stirred at 20°C during 10 min. This mixture was added to a solution of 3-quinoline carboxylic acid (160 mg, 0.92 mmol), BOP (488 mg, 1.10 mmol) and triethylamine (384 µL, 2.76 mmol) in dimethylformamide (8.5 mL). The resulting solution was stirred at 20°C for 12 h. Water (18 mL) was added and the aqueous phase was extracted with dichloromethane (3x20 mL). The combined organic phases were washed with water. The precipitate formed was filtered, washed with dichloromethane and dried to give **9** (117 mg, 25%) as a white solid. m. p.: 194-196°C. ^{1}H NMR (400.13 MHz, DMSO-*d6*): δ 9.28 (d, *J* = 2.2 Hz, 1H), 8.81 (d, *J* = 1.9 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 2H), 7.87 (t, *J* = 8.2 Hz, 1H), 7.72-7.68 (m, 2H), 7.61 (d, *J* = 7.0Hz, 1H), 7.31 (d, *J* = 7.8Hz, 1H), 7.14 (t, *J* = 7.8Hz, 1H), 4.35 (s, 2H), 3.35 (t, *J* = 6.8 Hz, 2H), 2.25 (t, *J* = 7.1 Hz, 2H), 1.82 (qt, *J* = 7.1 Hz, 2H). ^{13}C NMR (100.6 MHz, DMSO-*d6*): *δ* 174.3, 167.9, 159.1, 149.0, 148.4, 135.9, 135.4, 131.1, 130.6, 129.1, 128.8, 127.4, 127.2, 126.6, 95.3, 48.6, 35.6, 29.0, 24.1. IR (cm^{-1}): 1640, 1593, 1539, 1442, 740, 670. HRMS (ESI^{+}): calcd for $C_{22}H_{23}IN_5O_2$ [M+H]$^{+}$ 516.0897; found 516.0887. MS/MS (ESI^{+}): m/z (%) = 516 (92%), 276 (100%), 241 (13%), 156 (5%). HPLC: Column: Gemini C18 5µm 110Å 250x4.6 mm, eluent: acetonitrile/sodium phosphate dibasic 10 mM (40/60), flow: 1 mL/min, λ: 254 nm, t_R = 8.1 min.

3-(((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)-1-methylquinolin-1-ium trifluoromethanesulfonate (10). Under argon, **4e** (1 g, 3.7 mmol) was dissolved in 10 mL dry dichloromethane and methyl trifluoromethanesulfonate (486 µL, 4.4 mmol) was added. The mixture was stirred at 20°C during 4 hours. Diethyl ether was added and the precipitate was filtered and dried under vacuum to give **10** as a white solid (1.54 g, 96%). m. p.: 154°C. ^{1}H NMR (300 MHz, DMSO): *δ* 10.20 (s, 1H), 10.10 (s, 1H), 8.75 (d, *J* = 8.1 Hz, 1H), 8.64 (d, *J* =

8.9 Hz, 1H), 8.49 (t, J = 7.8 Hz, 1H), 8.20 (t, J = 7.5 Hz, 1H), 4.77 (s, 3H), 3.01 (s, 4H). ^{13}C NMR (75 MHz, DMSO): δ 169.9, 158.8, 150.6, 149.4, 140.1, 139.0, 132.6, 131.2, 128.4, 120.7 (q, J = 320.3 Hz), 119.6, 118.7, 45.7, 25.7. HRMS (ESI$^+$): calculated for $C_{15}H_{13}N_2O_4^+$ [M]$^+$ 285.0870; found 285.0870; IR (cm^{-1}) 1778, 1727, 1193, 1028, 778, 636.

3-((4-(3-(3-iodobenzyl)guanidino)-4-oxobutyl)carbamoyl)-1-methylquinolin-1-ium acetate (2d). Under argon, **10** (60 mg, 0.14 mmol) and **8b'** (33 mg, 0.07 mmol) were stirred in dry tetrahydrofuran (4 mL). DBU-polymer bond (119 mg, 0.14 mmol) was added and the mixture was stirred overnight at 20°C. The solution was filtered and the solvent was removed by vacuum. The crude product was purified with a C18-reversed phase silica gel using a semi preparative Pursuit XRS 250x4.6 mm; 5 µm at 15 mL.min^{-1} with phosphate buffer (10 mM)/acetonitrile gradient from 95%-5% to 70%-30% to give **2d** as green oil (27 mg, 58%). ^{1}H NMR (300 MHz, MeOD): δ 9.78 (s, 1H), 9.56 (s, 1H), 8.57 (d, J = 9.0 Hz, 1H), 8.49 (d, J = 8.1 Hz, 1H), 8.39 (t, J = 7.5 Hz, 1H), 8.14 (t, J = 7.6 Hz, 1H), 7.70 (s, 1H), 7.65 (d, J = 7.0 Hz, 1H), 7.33 (d, J = 7.7 Hz, 1H), 7.14 (t, J = 7.7 Hz, 1H), 4.75 (s, 3H), 4.65 (s, 4H), 4.43 (s, 2H), 3.56 (t, J = 6.8 Hz, 2H), 2.58 – 2.46 (m, 2H), 2.10–1.96 (m, 2H). ^{13}C NMR (75 MHz, MeOD): δ 180.2, 175.3, 163.9, 158.9, 150.9, 146.4, 140.6, 140.5, 138.5, 138.1, 137.3, 132.8, 132.1, 131.7, 130.3, 129.5, 127.6, 120.0, 95.2, 46.5, 44.5, 40.7, 32.0, 25.6, 23.9. HRMS (ESI$^+$): calcd for $C_{23}H_{25}IN_5O_2^+$ [M]$^+$ 530.1047; found 530.1057. IR (cm^{-1}) 2923, 1651, 1544, 1399, 649. HPLC with Synchronis C18 column 250x4.6mm; 5µm eluent acetonitrile/ammonium acetate buffer (20mM) 20/80, flow 1 mL.min^{-1}, λ = 242 nm, t_R = 5.1 min.

N-(4-(3-(3-iodobenzyl)guanidino)-4-oxobutyl)-1-methyl-1,4-dihydroquinoline-3-carboxamide (1d). Under argon, **2d** (20 mg, 0.03 mmol) was placed in degassed dry dichloromethane (1 mL) and BNAH[26] (6 mg, 0.03 mmol) was added. The mixture was stirred

at 20°C during 4 hours. The mixture was diluted with dichloromethane (1 mL) and the organic phase was washed with water (3×10 mL), dried over Na_2SO_4, filtered and concentrated to give **1d** as an orange oil (12 mg, 77%). ^{1}H NMR (300 MHz, MeOD): δ 7.69 (s, 1H), 7.61 (d, J = 6.7 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H), 7.12–7.08 (m, 3H), 7.02 (d, J = 6.8 Hz, 1H), 6.92 (d, J = 7.4 Hz, 1H), 6.82 (d, J = 8.1 Hz, 1H), 4.39 (s, 2H), 3.70 (s, 2H), 3.37–3.33 (m, 2H), 3.22 (s, 3H), 2.34 (t, J = 7.2 Hz, 2H), 1.93–1.84 (m, 2H). ^{13}C NMR (75 MHz, MeOD): δ 170.4, 168.1, 141.7, 141.6, 140.5, 140.5, 137.3, 131.5, 130.4, 128.5, 128.4, 127.6, 123.8, 123.7, 123.2, 113.7, 100.2, 44.7, 39.9, 39.1, 32.2, 27.2, 26.1. HRMS (ESI$^+$): calculated for $C_{23}H_{27}IN_5O_2$ $[M+H]^+$ 532.1209; found 532.1218. IR (cm^{-1}) 2921, 1658, 1101, 615. HPLC with Synchronis C18 column 250x4.6mm; 5µm eluent acetonitrile/ammonium acetate buffer (20mM) 20/80, flow 1 mL.min^{-1}, λ = 242 nm, t_R = 12.5 min.

Radiochemistry

Commercial reagents and solvents (Sigma Aldrich) of analytical grade were used without further purification. The radiosyntheses and purification of the radiolabeled compounds were performed in hot cell using an automatic apparatus (GE Healthcare TRACERlab FX-MeI and FX-M). [^{11}C]Methane was produced in a IBA cyclotron (Cyclone 18/9) by bombardment of a nitrogen gas target containing 10% of H_2 with 18 MeV protons (^{14}N(p,α)^{11}C reaction). [^{11}C]Methyl iodide was prepared from [^{11}C]methane by gas-phase iodination. [^{11}C]Methyl triflate was obtained by sweeping the [^{11}C]methyl iodide vapor through a column containing silver-triflate-impregnated graphitized carbon and heated at 180°C.[27] Analytical HPLC was realized on a system equipped with Merck-L200 pump and a Merck L-4250 detector in series with a Novelec β-flow detector.

Radiosynthesis of [^{11}C]1b. [^{11}C]Methyl triflate was trapped at 20°C during 8 min in a solution containing the quinoline **5b** (2 mg, 4.65 μmol) in acetonitrile (350 μL). Then, a solution of BNAH (6 mg, 27.9 μmol) in CH_3CN (200 μL) was added to the mixture. The resulting mixture was kept at 20°C for 5 min. Ammonium acetate 10mM (400 μL) was added to the crude reaction mixture before injection onto the HPLC system. The purification was performed by reverse-phase semipreparative HPLC (Phenomenex Gemini column 10 mm x 250 mm, 4 mL/min, λ=254 nm, CH_3CN/$AcONH_4$ 10mM 40:60). The fraction containing the labeled product [^{11}C]**1b** (t_R = 12.5 min) was collected into a flask containing water (50 mL) and passed through a solid phase extraction cartridge (Seppak tc18 short, Waters). [^{11}C]**1b** was eluted with ethanol (1 mL), and diluted with an isotonic saline solution (9 mL). The radiolabeled product was filtered through a sterile filter 0.22 μm. The radiochemical and chemical purities were determined by reverse-phase analytical HPLC (Phenomenex Gemini column 4.6 mm x 250 mm, 1 mL/min, λ =254 nm, CH_3CN/$AcONH_4$ 10mM 40:60, t_R[^{11}C]**1b** = 11 min). Radiochemical purity of [^{11}C]**1b** exceeded 99% and batches of 148-353MBq were ready for injection in about 55 min.

Radiosynthesis of [^{11}C]1c. [^{11}C]Methyl triflate was trapped at 20°C during 8 min in a solution containing the quinoline **5c** (2 mg, 4.36 μmol) in acetonitrile (350 μL). Then, a solution of BNAH (6 mg, 27.9 μmol) in CH_3CN (200 μL) was added to the mixture. The resulting mixture was kept at 100°C for 5 min. Ammonium acetate 10mM (400 μL) was added to the crude reaction mixture before injection onto the HPLC system. The purification was performed by reverse-phase semipreparative HPLC (Phenomenex Gemini column 10 mm x 250 mm, 5 mL/min, λ=254 nm, CH_3CN/$AcONH_4$ 10mM 35:65). The fraction containing the labeled product [^{11}C]**1c** (t_R = 12 min) was collected into a flask containing water (50 mL) and passed through a solid phase extraction cartridge (Seppak tc18 short, Waters). [^{11}C]**1c** was eluted with

ethanol (1 mL), and diluted with an isotonic saline solution (9 mL). The radiolabeled product was filtered through a sterile filter 0.22 µm. The radiochemical and chemical purities were determined by reverse-phase analytical HPLC (Phenomenex Gemini column 4.6 mm x 250 mm, 1 mL/min, λ =254 nm, $CH_3CN/AcONH_4$ 10mM 35:65, t_R[^{11}C]**1c** = 9.5 min). Radiochemical purity of [^{11}C]**1c** exceeded 99% and batches of 185-333MBq were ready for injection in about 55 min.

Radiosynthesis of [^{11}C]1d. [^{11}C]Methyl triflate was trapped at 20°C during 8 min in a solution containing the quinoline **9** (2 mg, 4.24 µmol) in acetonitrile (350 µL). Then, a solution of BNAH (6 mg, 27.9 µmol) in CH_3CN (200 µL) was added to the mixture. The resulting mixture was kept at 20°C for 10 min. Ammonium acetate 10mM (300 µL) was added to the crude reaction mixture before injection onto the HPLC system. The purification was performed by reverse-phase semipreparative HPLC (Phenomenex Gemini column 10 mm x 250 mm, 4 mL/min, λ=254 nm, CH_3CN/H2O 50/50 +0.01% NEt_3). The fraction containing the labeled product [^{11}C]**1d** (t_R = 14.5 min) was collected into a flask containing water (50 mL) and passed through a solid phase extraction cartridge (Chromabond C18 ec, Macherey Nagel). [^{11}C]**1d** was eluted with ethanol (400 µL), and diluted with an isotonic saline solution (4 mL). The radiolabeled product was filtered through a sterile filter 0.22 µm. The radiochemical and chemical purities were determined by reverse-phase analytical HPLC (Phenomenex Gemini column 4.6 mm x 250 mm, 1 mL/min, λ =254 nm, CH_3CN/H_2O 60:40, t_R[^{11}C]**1d**= 12 min). Radiochemical purity of [^{11}C]**1d** exceeded 99% and batches of 185-518MBq were ready for injection in about 60 min.

Biological evaluation of [^{11}C]1b-d

Animals. The animal investigations were performed under the European directive (86/609/EU) and the French National Committee (decret 87/848) for the care and use of laboratory animals (GIP Cyceron; approval D14-118-001). Permission was sought and obtained for all experimental procedures from the regional committee on animal ethics (CENOMEXA 1112.17). Sprague Dawley male rats weighing 230-553 g were used in all experiments. The animals were kept at constant temperature (22°C) and humidity (50%) with 12 h light/dark cycles and were allowed free access to food and water until experiment time. Anesthesia was induced with 5% isoflurane in a gas mixture of nitrous oxide/oxygen (70/30%) and maintained with 1.5-2% isoflurane without surgery. They were placed on a heating pad (37.5°C). A catheter was inserted into the tail vein.

Radioactivity uptake in rat brain. Rats were injected with [^{11}C]**1b-d** (6-47 MBq) formulated in a solution containing NaCl 0.9%/ethanol (v/v 90/10) and were killed by decapitation at different times post injection (5 to 45 min). Whole brain was quickly dissected and rinsed with saline solution to minimize residual blood. The brain sample was weighed, and the radioactivity was measured in a γ-counter (Cobra 2 gamma counter, Packard). Data were expressed as the percentage of injected dose (decay-corrected) per gram of tissue (% ID/g).

HPLC Analyses in rat blood and brain samples. Rats were injected with [^{11}C]**1b-d** (6-47 MBq) formulated in a solution containing NaCl 0.9%/ethanol (v/v 90/10) and were sacrificed at various time points after the administration (5 to 45 min). Whole brain was quickly dissected, crushed (UltraTurrax T25, Janke and Kunkel) in acetonitrile (2.5 mL) and centrifuged (4024 x g, 7 min, 4°C). Intracardiac blood sample was collected and after centrifugation (4024 x g, 3 min, 4°C), plasma was mixed with an equivalent volume of acetonitrile and centrifuged (4024

x g, 7 min, 4°C). For each sample, the radioactivity of the precipitate was measured to quantify the efficiency of the acetonitrile extraction. Supernatants were filtered and injected onto HPLC (conditions identical to reverse-phase semipreparative purification of [^{11}C]**1b-d**). The detected peaks were integrated and their areas were expressed as a percentage of the sum of areas of all radioactive compounds present (decay-corrected).

Reference Section

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